Featured research

Abstracts and commentaries

The pH hypothesis of postconditioning. Staccato reperfusion reintroduces oxygen and perpetuates myocardial acidosis

Cohen MV, Yang X-M, Downey JM. *Circulation*. 2007;115:1895–1903.

Timely reperfusion salvages myocardium from tissue injury after prolonged ischemia. However, there is convincing evidence that sudden restoration of blood flow to ischemic myocardium may paradoxically exaggerate injury that is not present at the end of ischemia. A few years ago the evidence was presented that, in anesthetized open-chest dogs, several very brief coronary occlusions immediately after relief of a prolonged occlusion (ie, postconditioning) significantly reduced infarct size [1]. The degree of myocardial salvage with postconditioning was comparable to that observed with preconditioning. Postconditioning is protective in animals http://circ.ahajournals.org/cgi/content/full/115/14/1895 and has had beneficial functional effects in patients who underwent coronary angioplasty for acute coronary occlusion. Until we understand its mechanism, however, it will be impossible to design an optimal postconditioning procedure.

The formation of mitochondrial permeability transition pores (MPTPs) leads to catastrophic consequences for reperfused cells, such as necrosis and apoptosis. Preconditioning suppresses the formation of MPTPs early in reperfusion as does postconditioning. In addition, cyclosporin A, which is a closer of MPTPs, is cardioprotective when infused at reperfusion, whereas atractyloside, which opens MPTPs, aborts the protection of preconditioning. Because acidosis prevents the formation of MPTPs by blocking Ca^{2+} binding to adenine nucleotide translocase (a component of MPTP) and displacing cyclophilin from it, the authors speculated that postconditioning might prevent the formation of MPTPs by maintaining acidosis during the first minutes of reperfusion.

Commentary

After 30 min of regional ischemia in isolated rabbit hearts, reperfusion with buffer at physiological pH (7.4) caused $34.4 \pm 2.2\%$ of the risk zone to infarct, whereas 2 min of postconditioning (six cycles of 10 s reperfusion/10 s occlusion) at reperfusion resulted in $10.7 \pm 2.9\%$ infarction. One minute (three cycles) of postconditioning was not protective. Hypercapnic (ie, mildly acidic) buffer (pH 6.9) for the first 2 min of reperfusion in lieu of postconditioning caused equivalent cardioprotection ($15.0 \pm 2.6\%$ infarction), whereas 1 min of acidosis did not protect. Delaying postconditioning (six cycles) aborted protection. Reperfusion with alkaline buffer (pH 7.7) blocked postconditioning protection, but addition of the MPTP closer, cyclosporin A, restored protection. The protein kinase C antagonist, chelerythrine, and the mitochondrial K_{ATP} channel closer, 5-hydroxydecanoate, each blocked protection from 2 min of acidosis, as they did for postconditioning.

This study points to an important aspect of intracellular pH in controlling mitochondrial signals for protection of cardiomyocytes against reperfusion injury. Acidic perfusion had to be commenced immediately after release of the coronary occlusion. Indeed, myocardium becomes acidic during ischemia, but this acidosis is quickly relieved after reperfusion. MPTPs that could not open in an acidic milieu during ischemia quickly open as pH increases upon reperfusion. Opening of MPTPs leads to collapse of the mitochondrial transmembrane potential, cessation of ATP production, and subsequent cell death.

REFERENCE

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Danielle Feuvray

Inhibition of free fatty acids metabolism as a therapeutic target in patients with heart failure

Fragasso G. *Int J Clin Pract*. 2007;61:603–610.

Recent studies have provided evidence that alterations in cardiac metabolism can be present in several cardiac syndromes. In heart failure, wasting of subcutaneous fat and skeletal muscle is relatively common, and suggests an increased utilization of non carbohydrate substrates for energy metabolism. In fact, fasting blood ketone bodies, in addition to fat oxidation during exercise, have been shown to be increased in patients with heart failure. This metabolic shift determines a reduction in myocardial oxygen consumption efficiency. A direct approach to manipulate cardiac energy metabolism consists in modifying substrate utilization by the heart. To date, the most effective metabolic treatments include several pharmacological agents that directly inhibit fatty acid oxidation. Clinical studies have shown that these agents can substantially increase the ischemic threshold in patients with effort angina. However, the findings of current research are also supporting the concept that shifting the energy substrate preference away from fatty acid metabolism and towards glucose metabolism could be an effective adjunctive treatment in patients with heart failure, in terms of improvement in left ventricular function and glucose metabolism. In fact, these agents have also been shown to improve overall glucose metabolism in diabetic patients with left ventricular dysfunction. In this paper, the recent literature on the beneficial therapeutic effects of modulation of the utilization of cardiac metabolic substrates in patients with heart failure is reviewed and discussed.

Commentary

The need to improve the management of heart failure is widely recognized, even though many advances have been made over the past decade.

The metabolic approach to heart failure is assuming increasing importance. Fragasso reviews in detail a metabolic approach that has the inhibition of free fatty acid metabolism as the therapeutic target. We know myocardial energy metabolism may be normal in the early stages of heart failure, but, as the failure progresses, mitochondrial oxidative metabolism is reduced and glycolysis is increased, with downregulation of glucose and fatty acid oxidation. With the evidence that reducing fatty acid oxidation at the same time as increasing glucose oxidation can improve cardiac function and slow the progression of heart failure has come the concept of metabolic manipulation with drugs designed to inhibit fatty acid oxidation and simultaneously promote glucose oxidation.

The most widely studied metabolic agent is trimetazidine, which inhibits 3-ketoacyl coenzyme A thiolase, the last enzyme involved in β-oxidation. Importantly, trimetazidine has also shown good experimental evidence of efficacy, and important subjective and objective evidence of benefit in patients with heart failure. It is effective when used in addition to current-evidence based treatments, with minimal adverse effects and no drug interactions. The documented improvement in ejection fraction with this drug may be prognostically important, but this is as yet unproven (although the findings of one small study are very encouraging).

Fragasso's excellent review sets the benchmark for the use of a metabolic approach to the treatment of heart failure. Both Fragasso and I are in agreement that the ''time has come to test this huge potential therapeutic advancement in heart failure syndromes which still suffer high morbidity and mortality''. The potential to prolong life and with an improved quality is the optimal medical target, giving patients with heart failure new hope for the future.

Graham Jackson

Postconditioning the human heart

Staat P, Rioufol G, Piot C, et al. *Circulation*. 2005;112:2143–2148.

In animal models, brief periods of ischemia performed just at the time of reperfusion can reduce infarct size – a phenomenon called postconditioning. In this prospective, randomized, controlled, multicenter study, we investigated whether postconditioning may protect the human heart during coronary angioplasty for acute myocardial infarction. Thirty patients, submitted to coronary angioplasty for ongoing acute

myocardial infarction, took part in the study. Patients were randomly assigned to either a control or a postconditioning group. After reperfusion by direct stenting, control patients underwent no further intervention; in the other group, postconditioning was performed within 1 min of reflow by four episodes of 1 min of inflation and 1 min of deflation of the angioplasty balloon. Infarct size was assessed by measuring total creatine kinase release over 72 h. Area at risk and collateral blood flow were estimated on left ventricular and coronary angiograms. No adverse events occurred in the postconditioning group. Determinants of infarct size, including ischemia time, size of the area at risk, and collateral flow, were comparable between the two groups. The area under the curve of creatine kinase release was significantly reduced in the postconditioning group compared with controls (averages of $208\,984 \pm 26\,576$ arbitrary units (AU) and $326\,095 \pm 48\,779$ AU, respectively) representing a 36% reduction in infarct size. Blush grade, a marker of myocardial reperfusion, was significantly increased in the postconditioned group compared with controls: 2.44 ± 0.17 and 1.95 ± 0.27, respectively ($P < 0.05$). These findings suggest that postconditioning by coronary angioplasty protects the human heart during acute myocardial infarction.

Commentary

Reperfusion is the definitive treatment to salvage ischemic myocardium from infarction. A primary determinant of infarct size is the duration of ischemia. In myocardium that has not been irreversibly injured by ischemia, reperfusion induces additional injury in the area at risk. The heart has potent innate cardioprotective mechanisms against ischemia-reperfusion that reduce infarct size and other presentations of postischemic injury. Ischemic preconditioning applied before the prolonged ischemia exerts the most potent protection observed among known strategies. It has been assumed that it exerts protection during ischemia. However, recent data suggest that cardioprotection is also exerted during reperfusion. Postconditioning, defined as brief intermittent cycles of ischemia alternating with reperfusion applied after the ischemic event, has been shown to reduce infarct size, in some cases equivalent to that observed with ischemic preconditioning.

Although there are similarities in mechanisms of cardioprotection by these two interventions, there are key differences that go beyond simply exerting these mechanisms before or after ischemia. A significant limitation of ischemic preconditioning has been the inability to apply this maneuver clinically, except in situations in which the ischemic event can be predicted. In contrast, PoC is applied at the point of service in the hospital (catheter laboratory for percutaneous coronary intervention, coronary artery bypass grafting and other cardiac surgery) where and when reperfusion is initiated. Initial clinical studies are in agreement with the success and extent to which postconditioning reduces infarct size and myocardial injury, even in the presence of several comorbidities.

Percutaneous transluminal coronary angioplasty postconditioning is possibly not the easiest, and probably not the best, solution for all patients with acute myocardial infarction, and several questions remain to be addressed, including whether postconditioning protects the hearts of patients with comorbidities (diabetes, hyperlipidemia, age), the window of time for its application in humans, and whether it improves functional recovery and clinical outcome. We believe that pharmacological postconditioning is the most promising approach. Administration, at the time of reperfusion, of a given drug that will mimic ischemic postconditioning will make this protection available to all patients with acute myocardial infarction. An open question remains the route of administration of the protective agent. If reperfusion damage, mediated by oxygen free radicals, occurs instantaneously at the return of oxygenated blood in the ischemic territory, then the only means of successfully preventing reperfusion damage will be ''preloading'' the area with the protective agent (eg, adenosine) before vessel recanalization.

Mario Marzilli